FIGURE 1 Echocardiographic Determinants of Fitness Response to Exercise Training

A

Subject Characteristics	Exercise Training Responders (n = 101)	Exercise Training Non-responders (n = 46)	p Value
Change in Peak absolute VO2 l/min, range	0.14 (0.11)	-0.07 (0.07)	<0.01
Age , years	56.5 (6.2)	57.5 (6.8)	0.437
Exercise Training Groups 4 kcal/kg/week (%) 8 kcal/kg/week (%) 12 kcal/kg/week (%)	40.6 31.7 27.7	69.6 19.6 10.9	0.004
African Americans (%)	40.6	45.6	0.38
Body mass index, kg/m^2	31.3 (3.4)	32.5 (3.5)	0.02
Baseline exercise systolic BP, mm Hg	178 (20)	181 (24)	0.67
Baseline peak absolute VO2, l/min	1.24 (0.25)	1.34 (0.23)	0.01
Adherence (%) Median (IQR)	100 (99-100)	99.98 (97.1-100)	0.23

B

Echocardiographic Characteristics[#]	Odds Ratio	95% CI
Inter-ventricular Septal Thickness	2.02	1.26 – 3.26
Posterior Wall Thickness	1.92	1.19 – 3.10
Relative Wall Thickness	1.77	1.15 – 2.72
Indexed Left Ventricular Mass[¥]	1.70	1.04 – 2.78

[#]Each echo parameter was included in a separate logistic regression analysis model adjusted for age, body mass index, systolic blood pressure, baseline fitness, exercise training dose and adherence to exercise training. [¥]Indexed to allometric height.

(A) Baseline characteristics of study participants stratified by training response. **(B)** Association between baseline echocardiographic measurements and nonresponse to exercise training. Values are mean (SD) or %, unless otherwise noted. BP = blood pressure; CI = confidence interval; IQR = interquartile range; VO2 = volume of oxygen consumed.

may be better suited to adapt to exercise with physiological remodeling as compared to those with adverse LV remodeling at baseline.

Our study findings could have important implications. The present study suggests that low fit participants with adverse LV remodeling, who are at a greater risk for nonresponse to exercise, may require alternative exercise training strategies (e.g., higher intensity and/or dose of exercise training) to improve fitness.

Our study represents an important step in this direction with characterization of distinct cardiac phenotypes associated with heterogeneity in response to exercise training. Further studies are needed to characterize the underlying cardiovascular mechanisms and optimal treatment for the nonresponse to moderate-intensity exercise training.

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Aortic Calcifications Present the Next Challenge After TAVR

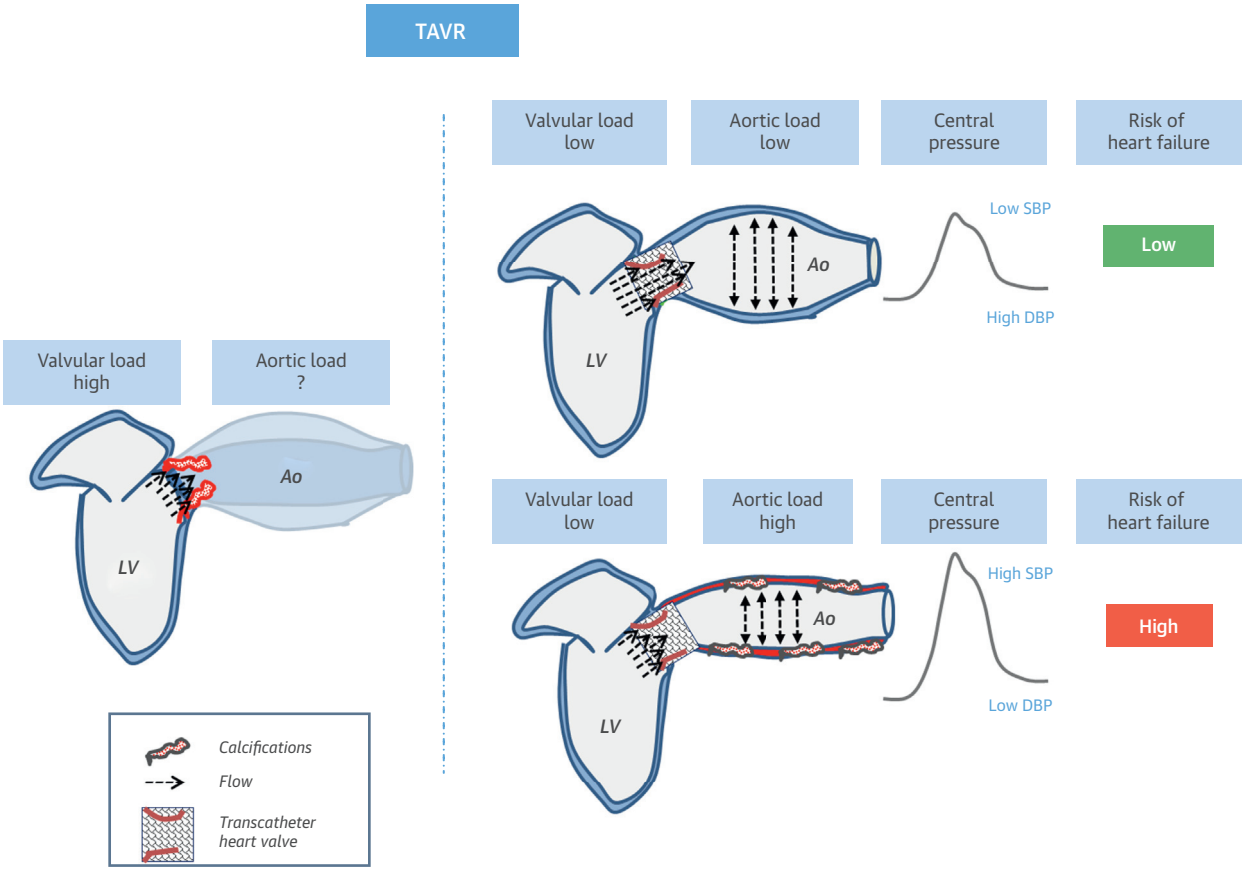
In the presence of aortic stenosis, the left ventricle (LV) faces a double challenge: a valvular load and an arterial load (1). Transcatheter aortic valve replacement (TAVR) has now become a safe and

effective alternative to surgery in patients with a contraindication or at high risk (2). Because patients considered for TAVR are elderly, implying that they often have a markedly remodeled aorta, the arterial component of the LV load is likely to be sizable; yet, the precise impact of aortic remodeling on cardiac outcomes after TAVR has never been tackled. We examined the effect of ascending aortic calcifications (AAC) measured by computed tomography (CT) on a composite endpoint encompassing cardiac mortality (from heart failure [HF], myocardial infarction [MI], or sudden death) and hospitalization for HF following TAVR with Edwards Sapien devices (Edwards Lifesciences, Irvine, California) in 127 consecutive patients. Patients provided written informed consent and the study received ethical committee approval.

Image acquisition was performed on a Brilliance 64-slice CT scanner (Philips, Healthcare, North Andover, Massachusetts). Calcifications of the thoracic aorta were individually delineated from the aortic sinus to the left subclavian artery with a semi-automatic segmentation tool (IntelliSpace Portal, Philips Healthcare) (3). For each patient, the total volume of the delineated AAC was calculated.

AAC was considered in turn as a categorical variable (tertiles) and as a continuous variable for statistical analysis; AAC ranged from 0 to 21,700 mm^3. Transapical approach, peripheral artery disease, and previous coronary artery bypass graft surgery were more frequent with increasing AAC levels. No difference was observed for other variables, in particular comorbidities, Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), or ejection

FIGURE 1 **Impact of Aortic Calcifications on Cardiac Outcomes After TAVR**



Aortic stiffness is closely related to left ventricular (LV) function, but most of the preoperative work-up before transcatheter aortic valve replacement (TAVR) concerns valvular load **(left panel)**. Once the aortic stenosis is relieved, aortic (Ao) load becomes critical for LV function **(right panel)**. DBP = diastolic blood pressure; SBP = systolic blood pressure.

fraction (EF). After a median follow-up of 907 days (range 0 to 1,912 days), we observed 24 cardiac deaths (14 HF, 1 MI, 9 sudden death) and 46 hospitalizations for HF, leading to a total of 54 composite endpoints. Seven patients died during the first week and were considered as periprocedural events.

AAC markedly influenced the occurrence of the outcome in univariable analysis (tertiles 3 and 2 vs. 1 hazard ratio [HR]: 2.61; 95% confidence interval [CI]: 1.31 to 5.20; p = 0.006; +1 Log increment of ACC HR: 1.70; 95% CI: 1.15 to 2.50; p = 0.007). Potential confounders considered were either univariate predictors of events or significant correlates of AAC. In a first multivariable Cox regression model adjusted for arterial approach, peripheral artery disease, and previous coronary artery bypass grafting (or prevalence of coronary artery disease), AAC remained predictive of the outcome (tertiles 3 and 2 vs. 1 HR: 2.50; 95% CI: 1.23 to 5.09; p = 0.001; +1 Log increment of ACC HR: 1.70; 95% CI: 1.10 to 2.61; p = 0.016). Similar findings were observed in 2 other multivariable models, 1 adjusted for EuroSCORE and diabetes and the other adjusted for post-procedural grade 2 aortic regurgitation and calcification of the aortic ring. A sensitivity analysis performed after exclusion of periprocedural events led to similar results.

This study shows that the extent of AAC is a strong independent predictor of cardiac outcome after TAVR. This is not likely to be due to a higher occurrence of MI; indeed, outcome was mainly driven by HF while only 1 fatal MI was observed, which arose in the periprocedural period and was not accounted for in the sensitivity analysis. Furthermore, adjustments for "coronary history" did not change the results. We believe that the worse cardiac prognosis associated with a high AAC score mainly reflects the consequences of aortic stiffening on LV function (**Figure 1**) (4). This is probably critical in TAVR patients, because they often have aged vessels. For the moment, methods to "destiffen" the aorta are limited, and AAC should be considered primarily as a new powerful criterion to refine risk stratification in usually severely ill patients in whom the best option is not easy to determine.

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Considerations for Drug Development for Heart Failure

I read with great interest the thoughtful editorial by Greene and Gheorghiade (1) proposing rigorous testing in a small homogenous cohort of patients hospitalized with heart failure in early phase trials in order to elucidate the mechanisms of action and benefit for maximal pairing of the new therapy with subsequent phase III trial population. Considering that the last heart failure drug approved by the Food and Drug Administration was the combination of hydralazine and isosorbide dinitrate in 2005, this concept could be equally applied to outpatient heart failure population.

In assessing the merit of this innovative approach, however, 2 issues need to be taken into consideration:

1. Even if the new therapy is of proven benefit in the highly selected cohort, it will need to be tested in a wider less selected cohort and having more insight into the mechanism of action may not necessarily help in selecting a wider patient population.
2. Differences between trials and community patients have long been recognized (2) and adoption of the